REMARKS

Claims 18-24 are now pending. A list of the claims is provided in an appendix for the Examiner's convenience.

Objection to the Specification

The specification is objected to for improper incorporation of matter by reference, specifically to the incorporation of the disclosure of Lesage et al., FEBS Letters 353:37-42 (1994) (Lesage). Applicants disagree that this incorporation is improper because such restriction against incorporation of an article is only with regard to essential matter. As discussed further below, Applicants submit that the specification is sufficient to practice the claimed methods. However, without agreeing with the conclusion of the Office Action, an amended Sequence Listing accompanies the present response, along with a declaration in accordance with *In re Hawkins*, stating that SEQ ID NOS: 3-6 are identical to the sequences disclosed in Lesage et al. The right to explicitly incorporate any and all of the material from the parent application and Lesage et al. is reserved.

The specification is also objected to for lack of agreement between the figure legends and the drawings. As the Examiner points out, the drawings are informal. Formal drawings will be submitted after a finding of allowable claims. Applicants believe that the description of the informal drawings is sufficiently clear for examination purposes and necessary

amendments to make the description agree with the formal drawings will be made upon the determination of the format and submission of such drawings.

Obviousness-Type Double Patenting

Claim 18 is rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-19 of USPN 5,744,324 in view of Yatani et al, *Science* 235:207-211 (1987) (Yatani). Without necessarily agreeing with this conclusion (*see* below), Applicants submit herewith a Terminal Disclaimer disclaiming the terminal portion of the present patent that may extend beyond the life of USPN 5,744,324, as described therein. Therefore, the present rejection is moot and Applicants respectfully request that it be withdrawn.

Claim 18 is also rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-19 of USPN 5,734,021 (the '021 patent) in view of Yatani. Applicants respectfully traverse.

The standard for an obviousness-type double patenting rejection is the same as for a rejection under 35 U.S.C. § 103 (*see* MPEP § 804), except that only the claims and not the underlying disclosure of the issued patent may be considered as prior art. Therefore, for this rejection to be proper, the claims of the '021 patent and Yatani must 1) disclose each element of the presently claimed invention; 2) provide motivation to combine and modify these teachings to obtain the present invention ; and 3) provide a reasonable expectation of success in obtaining the present invention. These criteria are not met in the present rejection.

The present Claim 18 is directed to a method for screening for agents that inhibit the activity of a Kir3.0 channel by providing a functional heteromultimeric Kir3.0 channel , combining the agent and the channel under conditions that permit inward K+ current, and determining the induced current. The '021 patent claims KGA channel proteins that may be useful in the present invention. Yatani discloses inhibiting acetyl choline receptors with NAD and G proteins with pertussis toxin (PTX). Yatani does not teach or suggest methods for screening for agents that inhibit the activity of a Kir3.0 channel. In fact, Yatani show that the combination of NAD and PTX do not inhibit the activity of the K+ channel in their experiments, because addition of exogenous G protein showed that the channels were fully active. Therefore, the methods of the present invention are neither taught nor suggested. Without any indication that agents that could inhibit the activity of any K+ channel might even exist, no motivation can be found in the '021 patent claims and the prior art to combine these references and obtain the present invention, nor is any reasonable expectation that such methods could be obtained if the reference and claims were combined.

For the reasons discussed above, Claim 18 is not obvious over the claims of the '021 patent in view of Yatani. Therefore, Applicants respectfully request that this double patenting rejection be withdrawn.

Rejections Under 35 U.S.C. § 112

Claim 18 is rejected under 35 U.S.C. §112, first paragraph as containing subject matter not described in the specification such that it conveyed to the skilled artisan that the inventors had possession of the invention. Applicants respectfully traverse.

The thrust of this rejection is that heteromultimer species have been improperly incorporated by reference with the incorporation of the disclosure of Lesage. Applicants disagree with this rejection because, as mentioned above. Applicants submit that the specification is fully enabling for the skilled artisan to use the claimed method with any species of Kir3.0 channel, as further discussed below. As such, the literal disclosure of each potential Kir3.0 channel protein is not necessary. However, an amended sequence listing containing the Kir3.0 channel protein sequences disclosed in Lesage and a Declaration in accordance with *In re Hawkins* accompany the present response. Therefore, the present rejection is moot. applicants respectfully request that this 35 U.S.C. § 112, first paragraph rejection be withdrawn.

Claim 18 is rejected under 35 U.S.C. § 112, first paragraph as not being enabled by the specification. Applicants respectfully traverse.

The test of enablement is whether the specification provides sufficient information to practice the claimed method without undue experimentation. The present application does not claim Kir3.0 channel proteins. Rather, the rejected claim is to a method for screening for

agents that inhibit the activity of such channels. The specification provides ample instruction to identify the channels useful in the method. Examples of sources of proteins which may be part of the channel are provided (e.g., page 6, line 26 to page 7, line 1), as well as attributes of the functional channel will have (e.g., page 7, lines 1-8). The specification provides means of identifying components of the channel based on sequence identity (e.g., page 8, lines 5-14 and page 11, lines 1-8), as well as being encoded by nucleic acid with the ability to hibridize with disclosed sequences under low stringency conditions (e.g., page .11, lines 9-23). The identification of nucleic acid encoding protein components of the Kir3.0 channel used in the present method are elaborately described (*see* page 11, line 1 to page 13, line 19) as are various means for producing the channel (e.g., page 13, line 20 to page 14, line 16) and systems useful for identification (e.g., page 7, lines 21 to page 8, line 4). Several means of testing for induced current are also provided (e.g., page 17, lines 10-13).

For the reasons discussed above, the specification is enabling for practicing the method of Claim 18 with any Kir3.0 channel. Therefore, Applicants respectfully request that this 35 U.S.C. § 112, first paragraph rejection be withdrawn.

Claim 18 is rejected under 35 U.S.C. § 112, second paragraph as being indefinite for the recitation of the term Kir3.0. Applicants respectfully traverse.

As discussed above, the specification provides ample description to identify a Kir3.0 channel which may be used in the method of Claim 18. A Kir3.0 channel is defined both

physically and functionally. The physical and functional attributes of a Kir3.0 channel useful in the present method are easily identified by the skilled artisan without undue experimentation, due to the description in the specification and the general knowledge in the art. Once identified, the method may be used to screen for agents that inhibit its activity.

For the reasons discussed above, Claim 18 is not indefinite for the recitation of Kir3.0 and applicants respectfully request the withdrawal of this 35 U.S.C. § 112, second paragraph rejection.

Priority Date

The Office Acton states, "Claim 18 is non-obviously broader than claims in the parent application 08/066,372 and thus not entitled to the benefit of the earlier filing date." Applicants first point out that priority is dependent on the disclosure of the parent application, not the claims (*see* 35 U.S.C. § 120). Furthermore, unless the filing date of the earlier application is needed to overcome a reference, there is no need for such a determination to be made (*see* MPEP § 201.08). In this case, the present invention is non-obvious over all of the pertinent cited art; therefore the issue is moot. As such, applicants respectfully request that the consideration of priority be reserved until such time as a determination needs to be made.

Rejections Under 35 U.S.C. § 102

Claim 18 is rejected under 35 U.S.C. § 102(b) as being anticipated by Yatani. Applicants respectfully traverse.

For a rejection under 35 U.S.C. § 102 to be proper, each element of the rejected claim must be taught. Claim 18 is directed to a method for screening for agents that inhibit the activity of a Kir3.0 channel which involves providing a functional Kir3.0 channel formed from at least two Kir3.0 polypeptides, combining the agent and the channel under conditions that permit inward K+ current, and determining the induced current. A reduction in the induced current in the presence of the agent as compared with a control indicates that the agent inhibits Kir3.0 channel activity.

Yatani discloses agents that inhibit ACh receptors and G proteins. As discussed above, Yatani neither discloses nor suggests that agents that inhibit the K+ channel itself even exist, let alone providing a method for identifying such agents. In fact, Yatani showed that the activity of the K+ channels was independent of these agents (page 209, middle column, first paragraph), once conditions that permit inward K+ current were restored.

For the reasons discussed above, Yatani does not anticipate Claim 18. Therefore, Applicants respectfully request that this 35 U.S.C. § 102(b) rejection be withdrawn.

Claim 18 is rejected under 35 U.S.C. § 102(b) as being anticipated by Karschin et al., *PNAS, USA* 88:5694-5698 (1991) (Karschin). Applicants respectfully traverse.

As with Yatani, Karscin describes manipulation of receptors (5-HT type 1A) and G-proteins. This reference neither discloses nor suggests agents that inhibit the activity of a Kir3.0 channel, let alone a method such as described in Claim 18. Therefore, Claim 18 is not anticipated by Karschin and Applicants respectfully request that this rejection be withdrawn.

Claim 18 is rejected under 35 U.S.C. § 102(a) as being anticipated by Duprat et al., *Biochem. Biophys. Res. Com.* 212(2):657-663 (1995) (Duprat). Applicants respectfully traverse.

The standard for a proper § 102 rejection and a description of the elements of Claim 18 are discussed above. Duprat neither discloses nor suggests agents that inhibit the Kir3.0 heteromultimers of the present invention, let alone a method for screening for such inhibitors. The Office Acton points to manipulations of Mg++ and ATP described in the reference. applicants point out that activity was decreased in the absence of these. Neither Mg++ nor ATP can be described as inhibitors of a Kir3.0 channel, nor were they suggested to be. The Office Action points to the disclosure that coexpression of GIRK2 and GIRK3 resulted in no currents. Applicants respond that, therefore, a functional Kir3.0 channel was not provided, as required by the claim. GIRK1, GIRK2, etc. of Duprat are Kir3.0 polypeptides of the present claim, not agents. A GIRK2/3 heteromultimer that does not provide current under the conditions of the claim is not a functional Kir3.0 channel. GIRK3 is not an agent that inhibits the GIRK2 channel, as suggested by the Office Action.

For the reasons discussed above, Duprat does not anticipate Claim 18. Therefore Applicants respectfully request that this 35 U.S.C. § 102(a) rejection be withdrawn.

Applicants submit that the application is in form for allowance and early notice of such is requested. If the Examiner believes that there are remaining issues which may be resolved by telephone, he is urged to call the undersigned at (415) 781-1989.

Respectfully submitted,

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APPENDIX

18. A method for screening for agents that inhibit the activity of a Kir3.0 channel, the method comprising:

a) providing a functional Kir3.0 channel formed from at least two different inward rectifier, G-protein activated, mammalian, potassium Kir3.0 polypeptides;

b) combining the candidate agent with [a functional] said Kir3.0 channel under conditions that permit inward K+ current;

c) determining the induced current[;], wherein a reduction in said induced current in the presence of said agent as compared to a control is indicative that said agent inhibits the activity of a Kir3.0 channel.

Please add the following new claims:

--19. The method of Claim 18, wherein said Kir3.0 polypeptides are selected from the group consisting of polypeptides having at least about 50% amino acid sequence identity with Kir3.1, Kir3.2, Kir3.3 or Kir3.4.

20. The method of Claim 18, wherein said Kir3.0 polypeptides are selected from the group consisting of polypeptides encoded by nucleic acids that hybridize under low stringency conditions with a complement of a nucleic acid which encodes Kir3.1, Kir3.2, Kir3.3 or Kir3.4.

21. A method for screening for agents that inhibit the activity of a Kir3.0 channel, the method comprising:

a) providing a functional Kir3.0 channel formed by introducing into an expression host cell a nucleic acid encoding a first mammalian Kir3.0 polypeptide and a nucleic acid encoding a second mammalian Kir3.0 polypeptide under conditions that permit expression of said nucleic acid, wherein said first and second mammalian Kir3.0 polypeptides are different from each other, wherein said mammalian Kir3.0 polypeptides assemble to form a functional Kir3.0 in said expression host cell;

b) combining a candidate agent with a functional Kir3.0 channel under conditions that permit inward K+ current;

c) determining the induced current, wherein a decrease in said induced current in the presence of said agent as compared to a control is indicative that said agent inhibits the activity of a Kir3.0 channel.

22. The method of Claim 21, wherein said nucleic acid encoding said mammalian Kir3.0 polypeptides are selected from the group consisting of nucleic acids that hybridize under low stringency conditions with a complement of a nucleic acid which encodes Kir3.1, Kir3.2, Kir3.3 or Kir3.4.

23. A screening assay for identifying materials which inhibit the activity of a Kir3.0 channel, comprising the steps of:

(a) introducing nucleic acid encoding a Kir3.0 channel formed from at least two different inward rectifier, G-protein activated, mammalian, potassium Kir3.0 polypeptides into an expression system and causing the expression system to express said nucleic acid encoding a Kir3.0 channel;

(b) contacting the Kir3.0 channel with one or more candidate channel-inhibiting materials;

(c) selecting candidate material(s) which inhibit said activity relative to a control performed in their absence.

24. The method of Claim 23, wherein said nucleic acid encoding a Kir3.0 channel consists essentially of nucleic acids that hybridize under low stringency conditions with a complement of a nucleic acid which encodes Kir3.1, Kir3.2, Kir3.3 or Kir3.4.